## REMARKS

Reconsideration of this application is respectfully request.

Claims 1, 2 and 9-66 are presently pending in this application.

Claims 1, 2, 14-36 and 38 are amended herein. Claim 36 is amended and now provides the proper antecedent basis for the terms X1 and X2. Support for this amendment can be found in the specification and in claim 2. Claims 1, 2, 14-36 and 38 have been amended to correct minor errors, including the proper use of the connectors "and" and "or" and the addition of the phrase "in need of treatment". Support for these amendments can be found in the specification and claims as filed. No new matter has been added by these amendments.

Applicants request the addition of new claims 53-66. New claim 53 is supported by claim 38 as filed. Support for new claims 54 - 66 can be found in claims 39 – 51 as filed.

A paragraph on page 41 (paragraph 228) of the application beginning with the phrase "Scheme 1" was added to include the inadvertently admitted Scheme1: "Synthesis of Paclitaxel-macrolide hybrid." Support for Scheme 1 can be found in Scheme 1 in the provisional application, as filed, on page 30.

35 U.S.C. §112 First Paragraph

The Examiner has rejected claims 1 and 36-51 under 35 USC 112, first paragraph, stating that the specification, while being enabling for a linking group represented by the Formula IV, does not reasonably provide enablement for any linking group for the reasons set forth in the Office Action of August 10, 2004. The Examiner states that the specification fails to provide a specific definition for the linking group, and that the specification states that "L can be selected to be a linking group represented by the Formula IV," but that said definition is not limited to the group of Formula IV. The Examiner further states that the specification fails to provide any guidance or teaching on how to choose linking groups which do not have Formula IV. The Examiner maintains that the terminology "linking group" encompasses a large number of possible

groups, and that it would take an undue amount of experimentation to determine which specific linking groups will result in a compound having the desired activity.

This rejection is respectfully traversed. Claim 36 only is amended herein and is directed to compounds having a linking group of Formula IV. With respect to claim 1 and the claims dependent on it, Applicants submit that one of ordinary skill in the art is able to practice the full scope of the claimed invention described by these claims. See *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). "That is not to say that the specification itself must necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art." *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003).

The use of linkers (or "spacers") to link two parts of a conjugate was well known at the time the priority application was filed, in July 2002. Therefore, unlike nascent technology, enablement for linker technology does not have to be included within the specification because a person of ordinary skill in the art is familiar with linkers and will have knowledge of linkers independent from the patentee's instruction. *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247 (Fed. Cir. 2004).

Evidence that linkers are well known and understood in the art can be found by looking at similar U.S. patents. In a survey of patents using either the term "linker" or "spacer" in the claims, we retrieved 416 patents having composition, compound, delivery, or agent in the title.[1] Of the first 15 patents related to the chemical arts retrieved, 9 defined the spacer or linker used and 6 did not.[2]

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[1] Search performed at the USPTO Web site: (((ACLM/"a linker" OR ACLM/"a spacer") AND (((TTL/composition OR TTL/compound) OR TTL/deliver$) OR TTL/agent)) AND APD/19800101->20020701): Hits: 416 patents.

[2] The 6 patents are:
6,821,632 Composite of a vulcanizable rubber composition and cured rubber product
6,790,827 Bioconjugates and delivery of bioactive agents
6,787,517 Agent and methods for treating pain
6,783,819 Crown compound modified silica coatings for ink-jet media
6,777,237 Bioconjugates and delivery of bioactive agents
6,776,976 Bioconjugates and delivery of bioactive agents

Therefore, 40% of the patents (including the 20 issued most recently from applications prior to July 2002, and therefore subject to the current examination standards of the PTO) did not particularly define the linker or spacer in the broadest linker claim nor provide disclosure or enablement of all possible linkers in the specification. The relevant broad claims or claim sections of these patents are duplicated and presented collectively in Exhibit A. For example, U.S. Pat. 6,790,827 contains claim 24 directed to a method where the bioactive agent of claim 1 "is covalently bound indirectly to the cobalt atom of the organocobalt complex via a spacer." U.S. Pat. 6,787,517 claims an agent "wherein the therapeutic component and the targeting ligand are attached to each other through a spacer component" in claim 31.

Since the use of a broadly defined linker or spacer group was well-understood at the time this application was filed (as it was for these earlier-filed patents listed in footnote 2), the specification does not have to detail every possibility of the claimed linker to be enabling. Applicants therefore respectfully request reconsideration and withdrawal of this rejection. Nor do applicants ascribe to the activity or any other beneficial property of the claimed conjugates to the linker used to connect the two moieties. Thus, all a person of ordinary skill would have to do is device a linker that would react with and connect the macrolide moiety and the other steroid or alternative active moiety. It is submitted that this can readily be done in multiple ways with the exercise of a modicum of ordinary skill. Therefore, applicants respectfully request that this rejection be withdrawn.

The Examiner has rejected claim 45 under 35 USC 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth in the Office Action of August 10, 2004, i.e., there is no evidence of record that the antiviral compounds encompassed by the claim possess anti-HIV activity.

Applicants respectfully traverse. HIV and specific antiviral agents are disclosed in the specification (see page 5, line 5 – page 6, line 5). The use of many of these antiviral agents to treat HIV was known at the time this application was filed. Of the 16 antiviral agents that may be used in

claim 45, 11 are listed by the U.S. Public Health Service either singly or in combination with other antiviral agents as strongly recommended or an alternative agent for treating HIV.[3]

This demonstrates that the antiviral agents encompassed by claim 45 were known to possess anti-HIV activity before this application was filed. Further, claim 45 as originally filed teaches the use of compounds having a macrolide, linker, and antiviral subunit[4] for treating HIV. The combination of the teachings from the guidelines with the teachings of claim 45 would provide the treating physician with the knowledge that the compounds of claim 45 possess anti-HIV activity. Applicants respectfully request that this rejection be withdrawn.

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[3] Table 12 of the "Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents" published by the U.S. Public Health Service on February 04, 2002 entitled "Recommended Antiretroviral Agents for Initial Treatment of Established HIV Infection" (see Exhibit B; the full document can be found at *http://aidsinfo.nih.gov/guidelines/adult/archive/AA_020402.pdf*) lists the following antiviral agents:

| | |
|---|---|
| lamivudine | Part of a "strongly recommended" combination |
| ritonavir | Part of a "strongly recommended" combination |
| indinavir | Part of a "strongly recommended" combination |
| nevirapine | Strongly recommended |
| zidovudine | Part of a "strongly recommended" combination |
| didanosine | Part of a "strongly recommended" combination |
| stavudine | Part of a "strongly recommended" combination |
| abacavir | Recommended "as alternatives" |
| zalcitabine | Part of an "alternative" combination |
| amprenavir | Recommended "as alternatives" |
| ribavirin | part of strongly recommended combination |

[4] The original claim 44, from which claim 45 depends, originally included an anti-inflammatory steroid or non-steroid subunit, or an antineoplastic subunit in addition to the antiviral subunit. These subunits were removed from the claimed breadth of V in an amendment dated December 8, 2004.

35 U.S.C. §112 Second Paragraph

The Examiner has rejected claims 1, 2 and 9-52 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states that the terminology "and pharmaceutically acceptable salts and solvates thereof and individual diastereoisomers thereof" (claim 1) and "and pharmaceutically acceptable salts and solvates therefrom" (claims 2 and 14-35) is an improper Markush terminology. Claims 1, 2, and 14-36 have been amended and recite proper alternative limitations. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Examiner has rejected claim 2 as indefinite, asserting that it contains two definitions of the variable L. The Examiner states that adding the term "or" between the two definitions can be used to overcome the rejection. The Examiner further states that the term "and" or "or" should be added between the definitions (iii) and (iv) of the variable V in claims 2 and 36.

Claim 2 has been amended to recite a proper alternative limitation in the definition of **L** by adding the term "or." Additionally, several typographical errors have been corrected: the incorrectly labeled "(ii)" in the definition of **V** has been changed to "(iii)" and the phrase "may be" in the definition of L has been replaced with "is." Applicants are unsure of Examiner's intent in the rejection of claim 2 for the definition of the variables **V** since the definition of **V** contains the term "and" between definitions (iii) and (iv) (see bolded claim term and prior amendment page 12). Claim 36 has been amended to recite a proper alternative limitation in the definition of **V** by adding the term "and." Applicants respectfully request reconsideration and withdrawal of this rejection.

The Examiner asserts that the phrase "especially" in claim 38 renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention, and cites MPEP 2173.05(d). Claim 38 has been amended to delete the phrase "especially of diseases and conditions induced by or associated with an excessive secretion of TNF-α and IL-1." New claim 53, dependant on claim 38, limits the diseases and conditions to those induced by or

associated with an excessive secretion of TNF-α and IL-1. Support for this claim can be found in claim 38. Applicants respectfully request reconsideration and withdrawal of this rejection of claim 38.

Process claim 36 has been amended herein to correct an error with antecedent basis; this claim now contains antecedent basis for the terms X1 and X2. Support for this amendment can be found in claim 2.

Claim 52 has been amended to contain a final period.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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## EXHIBIT A

**Patents containing a broad linker or spacer**
*Patent, title, and representative claim(s) or claim sections*

6,821,632 Composite of a vulcanizable rubber composition and cured rubber product

16. A composite of a vulcanizable composition selected from a group consisting of natural rubbers, synthetic rubbers and thermoplastic elastomers and having a least one metal reinforcement element embedded therein, wherein the metal reinforcement element has a coating of a polymer deposited from a solution and compatible with and co-polymerizable with said vulcanizable composition, and bearing functional groups covalently bonding to the metal surface of said at least one reinforcement element, wherein the functional groups are selected from the group consisting of: ...R representing an organic **spacer** chain; ....

6,790,827 Bioconjugates and delivery of bioactive agents

24. The method of claim 1, wherein said bioactive agent is covalently bound indirectly to the cobalt atom of the organocobalt complex via a **spacer.**

25. The method of claim 24, wherein said spacer is a self-destructing **linker.**

6,787,517 Agent and methods for treating pain

31. An agent according to claim 1 wherein the therapeutic component and the targeting ligand are attached to each other through a **spacer** component.

6,783,819 Crown compound modified silica coatings for ink-jet media

6. A coated media substrate as in claim 1 wherein the crown compounds are attached to the reactive groups through **spacer** groups.

6,777,237 Bioconjugates and delivery of bioactive agents

1. 1. A method of administering a bioactive agent to cells of a targeted tissue site of a subject which comprises administering to said subject an effective amount of the bioactive agent as a bioconjugate, wherein said bioconjugate comprises the bioactive agent and an organocobalt complex ...wherein the bioactive agent is covalently conjugated to the cobalt atom of the organocobalt complex through a non-reactive atom in the bioactive agent molecule,....

31. The method of claim 1, wherein said bioactive agent is covalently bound is indirectly to the cobalt atom of the organocobalt complex via a **spacer**.

6,776,976 Bioconjugates and delivery of bioactive agents

1. A bioconjugate a bioactive agent and an organocobalt complex wherein the bioactive agent is covalently conjugated to the cobalt atom of the organocobalt complex through a non-reactive atom in the bioactive agent molecule, wherein said bioactive agent is selected from the group consisting of a peptide, a peptide analogue, a protein, protein analogue, a nucleic acid and a nucleic acid analogue.

6. The bioconjugate of claim 1, wherein said bioactive agent is covalently bound indirectly to the cobalt atom of the organocobalt complex via a **spacer**.

**Patents defining the linker or spacer**

6,835,807 Drug complex and drug delivery system
6,833,421 Compound
6,814,973 Cosmetic use of at least one polyorganosiloxane as a gelling agent and cosmetic composition containing it
6,780,969 Synthetic peptide composition as immunogens for prevention of urinary tract infection
6,777,557 Method and composition for rejuvenating cells, tissues organs, hair and nails
6,773,920 Delivery of functional protein sequences by translocating polypeptides
6,765,056 Aqueous cross-linkable binder composition and its use in the production of lacquer coatings
6,764,853 Method for targeted delivery of nucleic acids
6,762,223 Stabilized imageable coating composition and printing plate precursor

EXHIBIT B

# Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents

***February 4, 2002***

**Developed by the panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation**

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the **HIV/AIDS Treatment Information Service website** (http://www.hivatis.org).

# Table 12. Recommended Antiretroviral Agents for Initial Treatment of Established HIV Infection

This table provides a guide to the use of available treatment regimens for individuals with no prior or limited experience on HIV therapy. In accordance with the established goals of HIV therapy, priority is given to regimens in which clinical trials data suggest the following: sustained suppression of HIV plasma RNA (particularly in patients with high baseline viral load) and sustained increase in $CD4^+$ T cell count (in most cases over 48 weeks), and favorable clinical outcome (i.e., delayed progression to AIDS and death). Particular emphasis is given to regimens that have been compared directly with other regimens that perform sufficiently well with regard to these parameters to be included in the "Strongly Recommended" category. Additional consideration is given to the regimen's pill burden, dosing frequency, food requirements, convenience, toxicity, and drug interaction profile compared with other regimens.

It is important to note that all antiretroviral agents, including those in the "Strongly Recommended" category, have potentially serious toxic and adverse events associated with their use. The reader is strongly encouraged to consult tables 13–19 while formulating an antiretroviral regimen.

Antiretroviral drug regimens are comprised of one choice each from columns A and B. Drugs are listed in alphabetical, not priority, order.

| | | |
|---|---|---|
| **Strongly Recommended** | **Column A**<br>Efavirenz<br>Indinavir<br>Nelfinavir<br>Ritonavir + Indinavir*†<br>Ritonavir + Lopinavir*‡<br>Ritonavir + Saquinavir* (SGC§ or HGC§) | **Column B**<br>Didanosine + Lamivudine<br>Stavudine + Didanosine¶<br>Stavudine + Lamivudine<br>Zidovudine + Didanosine<br>Zidovudine + Lamivudine |
| **Recommended as Alternatives** | **Column A**<br>Abacavir<br>Amprenavir<br>Delavirdine<br>Nelfinavir + Saquinavir-SGC<br>Nevirapine<br>Ritonavir<br>Saquinavir-SGC | **Column B**<br>Zidovudine + Zalcitabine |
| **No Recommendation:** | Hydroxyurea in combination with antiretroviral drugs | |
| **Insufficient Data#** | Ritonavir + Amprenavir*<br>Ritonavir + Nelfinavir*<br>Tenofovir •• | |
| **Not Recommended:** | All monotherapies, whether from column A or B** | |
| **Should Not Be Offered** | **Column A**<br>Saquinavir-HGC †† | **Column B**<br>Stavudine + Zidovudine<br>Zalcitabine + Didanosine<br>Zalcitabine + Lamivudine<br>Zalcitabine + Stavudine |

* See page 14 for more information on optimizing protease inhibitor exposure with ritonavir.

† Based on expert opinion.

‡ Co-formulated as Kaletra.

§ Saquinavir-SGC, soft-gel capsule (Fortovase); Saquinavir-HGC, hard-gel capsule (Invirase).

¶ Pregnant women may be at increased risk for lactic acidosis and liver damage when treated with the combination of stavudine and didanosine. This combination should be used in pregnant women only when the potential benefit clearly outweighs the potential risk.

\# This category includes drugs or combinations for which information is too limited to allow a recommendation for or against use.

** Zidovudine monotherapy may be considered for prophylactic use in pregnant women with low viral load and high $CD4^+$ T cell counts to prevent perinatal transmission, as discussed under "Considerations for Antiretroviral Therapy in the HIV-Infected Pregnant Woman."

†† Use of Saquinavir-HGC (Invirase) is not recommended, except in combination with ritonavir.

•• Data from clinical trials are limited to use in salvage. Data from trials of Tenofovir as initial therapy may be available in the near future.